IMPLICATION OF CHRONIC STRESS AND DIABETES IN CEREBROVASCULAR DYSFUNCTION: A REVIEW STUDY

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmcay (Hons)

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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Ethics Statement

This study does not involve any human and animal trial.

Abstract

The aim of the review was to explore the effects of chronic stress and diabetes in cerebrovascular dysfunction and neurological disorder. The evidence of involvement of hyperglycaemia induced oxidative stress was found to be prominent to cause complications like vascular inflammation, and neurovascular impairments. The active participation of different chemokine, transcription factors and biochemical pathways/mechanisms were studied to breakdown the cross-talk between diabetes and cerebrovascular dysfunction. Thus, the main objective of this review is to explain the significant relationship between diabetes and cerebrovascular dysfunction by explaining the various biochemical pathways. This will be an aid to identify the role of oxidative, reactive oxygen species and genetic errors in progression of various co-morbidities. A better understanding of the correlation of chronic stress and diabetes may suggest alternate approaches to the treatment of neurological disorders through pharmaceutical interventions. Furthermore, studying the process by which oxidative stress affects the cerebro-vasculature and blood-brain barrier are essential for evaluating antioxidant therapies.

Keywords: Cerebrovascular dysfunction; chronic stress; diabetes; oxidative stress; reactive oxygen species; redox balance; gene regulatory network analysis.

Dedication

I want to dedicate this project to my respectable supervisors Dr. Eva Rahman Kabir, Professor and Chairperson, Department of Pharmacy, Brac University & Mohammad Kawsar Sharif Siam, Senior Lecturer, Department of Pharmacy, Brac University for their continuous and relentless guidance throughout my project.

Acknowledgement

I would like to proceed by thanking the Almighty Allah who is the source of our strength and knowledge which have enabled me to complete this project with full diligence.

I would like to showcase my deepest and most sincere gratitude to my project supervisor, Dr. Eva Rahman Kabir, Professor and Chairperson, Department of Pharmacy, Brac University, whose expertise, constant guidance, sincere monitoring and motivational approaches in every sphere have inspired me to conduct this project efficiently. I sincerely express my appreciation and admiration for her patience and provided sense of direction whenever I encountered complications throughout this phase.

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Lastly, I would like to thank my parents for their constant support and encouragement that further pushed me to work harder and face the difficulties during this time frame.

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List of Acronyms

CVS	Cerebrovascular Dysfunction
T2DM	Type 2 Diabetes Mellitus
BBB	Blood Brain Barrier
ROS	Reactive Oxygen Species
IL	Inter Leukin
MAPK	Mitogen Activated Protein Kinase
AD	Alzheimer's Disease
KEGG	Kyoto Encyclopedia of Genes and Genomes
CRP	C-Reactive Protein
TGF-β	Tumor Growth Factor-β

1. Introduction

Nervous system is a complex, sophisticated system acting as the central hub of the body. With the aid of neurons, axons, synapses and varieties of neurotransmitters, the brain, which is part of the nervous system, controls our movement, as well as receives and processes information. Stress is characterized by any events those are harmful for the normal functioning of the brain (Joëls, Marian, Baram, 2009). Any kind of traumatic injury or abnormalities can hinder the regular functioning of the nervous system. The study will primarily discuss the neurological dysfunction and alterations due to chronic stress and diabetes (Aarthy, Panwar, Selvaraj, & Singh, 2017).

People with co-morbidity are more prone to neurological disorder due to number of factors. Considering diabetes as the index disease, generally it prevails with depression, hypertension, renal problems and so on (Berge, Line Iden, Riise, 2015). Usually, in diabetic patients the circulation of blood to the brain, heart, and different organs including lower extremities is hindered, since atherosclerosis is a major implication which obstructs the arteries (Giacco & Brownlee, 2010). In case of cerebrovascular diseases, cerebral small vessel disease (CSVD), ischemic stroke, as well as hemorrhagic stroke are frequently observed (Zhou, Zhang, & Lu, 2014). Hyperglycemia, insulin resistance, obesity etc. are considered to be key contributors of cerebrovascular diseases occurrence. Chronic stress, hyperglycemia and other metabolic disturbance causes oxidative stress which eventually damages endothelium (Portik-Dobos, Anstadt, Hutchinson, Bannan, & Ergul, 2002a) . As the homeostasis is altered, there remains a great demand of energy to carry out the metabolic functions and brain suffers unwanted injury (Burrage, Marshall, Santanam, & Chantler, 2018). Chronic stress on the brain may cause permanent gene alteration, irregular firing of neurons, gene modification and expression. While short term stress can be reversible, chronic stress can bring about fatal neural dysfunctions of

brain (Joëls, Marian, Baram, 2009). Usually the hippocampus is responsible for the switching off the HPA stress response, but an atrophic or damaged hippocampus and damage or atrophy of the hippocampus fails or delays to switch off the HPA response during stress (McEwen, 2007).

This review will investigate the cross-talk between chronic stress, diabetes and cerebrovascular diseases. We will explore the influence of different mechanisms, pathways and cytokines responsible for the cerebrovascular complications (Zhou et al., 2014). Many studies have shown the risk of diabetes in the patients experiencing through chronic stress.

1.1 Cerebrovascular Dysfunction

Cerebrovascular dysfunction is considered as a life-threatening neurological events where diabetes, chronic stress, hypertension and smoking are the prominent factor responsible for the causalities. Globally cerebrovascular diseases are found to leave life-long impairments, resulting in the second leading cause of mortality. With improved lifestyle, cerebrovascular dysfunctions can be controlled to some extent, but with age the risk of occurrence of cerebrovascular diseases, such as ischemic and hemorrhagic strokes, vascular malformations and vascular dementia, increases to double (Benjamin et al., 2019). Chronic stress and diabetes can trigger strokes due to reduced cerebral blood flow, vessel narrowing, hypertension or embolism. The energy demand and hemodynamic changes are constantly controlled by Neuro-Vascular Coupling (NVC) where neurons, astrocytes and vascular cells are the main contributor of this auto regulatory process (Bloch, Obari, & Girouard, 2015). On the other hand, the duration of a stressful event has great impact on neuronal response and activation, release of neurotransmitters (Noradrenaline & serotonin), corticotrophin releasing hormones, steroid hormones (cortisol) etc. (Camacho, MariaVijitbenjaronk & Anastasio, 2019).

Table 1: Classification of Cerebrovascular Diseases

(Andjelkovic, Stamatovic, Phillips, Martinez-Revollar, & Keep, 2020).

Hemorhaggic Stroke	**Ischemic Stroke**	**Vascular Malformations**	**Stenosis**	**Vascular Dementia**	**Venous Angioma**
Intra-cerebral hemorrhage	Microvascular	Arteriovenous Malformation	Carotid	Cerebral small vessel disease	
Sub arachnoid hemorhage	Macrovascular	Cerebral Cavernous Malformation	Vertebral	Inherited cerebral small vessel disease	
	Transient Ischemic Attack		Intracranial		

1.2 Oxidative Stress

The human body copes and makes suitable adaptations to be able to deal with stressful events (Dragoş & Tănăsescu, 2010). These adaptations and alterations allow the brain to response in a different way to the newly adapted environment which includes alterations in neuronal activities (stress- response system) (Burrage, Emily, Marshall, KentL, Santanam, Nalini, Chantler, 2018) The autonomic nervous system (ANS), as well as the hypothalamic– pituitary–adrenal (HPA) are activated to maintain homeostasis (Murison, 2016), (Ford, 2009). This

adaptation mechanism is also known as allostasis which is continuously responding to daily challenges.

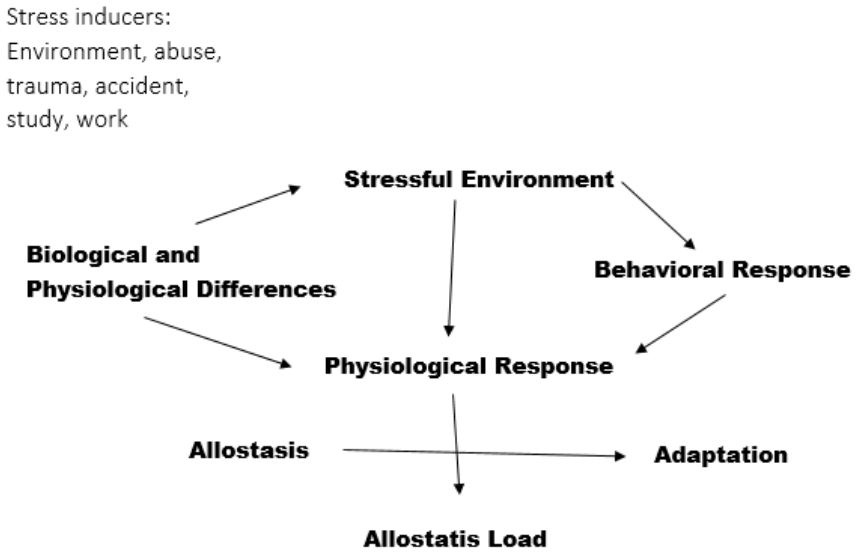

Figure 1: Central role of brain adapting stress.

(McEwen, 2007)

In Figure 1, we see that our brain experiences stress due environmental, physical and behavioral changes. Genetic defects, hostile surroundings, personal traumatic events, irregular and unhealthy food habit, smoking and drinking etc. are major factors that causes stress. Now, our brain adapts and cope up with this through allostasis (Gaab, J., Blättler, N., Menzi, T.Pabst, Stoyer, & Ehlert, 2003).

Each stress stimuli agitates a specific area of the CNS to generate desired response. But long term stress exposure, excessive workload or system failure can cause allostatic load, thus preventing to response in adverse condition (Wen, 1998). Allostatic load indicates neurological dysfunction and pathophysiological mechanisms, leading to depression in human (Burrage, Emily, Marshall, KentL, Santanam, Nalini, Chantler, 2018) Stress exposure are adaptive but chronic stress brings affects the brain.

Brain is the central organ of the nervous system where active metabolism takes place. Approximately 20% of total oxygen is used even when it is at resting stage. To carry out normal physiological actions, oxygen rich blood supply is needed. Any interruption in this process can bring about serious brain damage. During this consumption of high amount of oxygen by the brain, numerous free radicals, reactive oxygen species and nitrogen species are also produced (Díaz-Hung & González Fraguela, 2014). The brain requires O_2 to function any neural activity and alongside, it needs to carefully transform oxygen molecule to H_2O for backing up the ATP production (Cobley, Fiorello, & Bailey, 2018). Oxygen is considered to be dangerous because it can actively produce free radicals and non-radicals e.g. as superoxide (O_2^{-}), hydroxyl ($OH\cdot$), hydrogen peroxide (H_2O_2) (Cobley et al., 2018). Mitochondria produces these free radicals during cellular respiration (Aarthy et al., 2017). The brain is susceptible to irreversible neuronal damage by these species (cell death of brain cells e.g. neurons, glia, astrocytes) which leads to neuro-degeneration, as well as alterations in functional and structural characteristics of neurons. Some antioxidants such vitamin A (retinol), vitamin C (ascorbic acid), and vitamin E (tocopherol) are reported to detoxify and neutralize the negative effects of reactive oxygen species (ROS) (Varsha Shukla, Mishra, & Pant, 2011). There is distinct proof of the presence of limited amount of antioxidants, e.g., vitamin-E, and increased concentration of polyunsaturated fatty acids in post mortem human studies having major depressive disorders. Enzymes like glutathione peroxide, catalase, superoxide dismutase, aldehyde dehydrogenases, and sulfiredoxin are also known to be less active (Burrage, Emily, Marshall, KentL, Santanam, Nalini, Chantler, 2018). Any imbalance in the detoxification of ROS by the antioxidants is oxidative stress or imbalanced redox-state (Pizzino et al., 2017). Since neurons and glia are susceptible in increased oxidative stress, oxidative stress can be suggested to play a critical role in neurological dysfunction (Cobley et al., 2018).

1.3 Diabetes and Oxidative Stress

Diabetes is a disease where there is a deficit of insulin as a result of resistance to insulin or insufficient insulin secretion in the body. Both of the causes lead to hyperglycemia or increase of glucose concentration in blood. Hyperglycemia is responsible for oxidative stress and damaging endothelia (Zhou et al., 2014). The damage brings about a huge rush of cytokines and adhesion molecules, later inflammatory molecules accumulate in the wall of the vessels. Phagocytosis of low density lipoprotein cholesterol by macrophagocytes forms xanthoma cells. These xanthoma cells degenerates and turns into necrotic cells, simultaneously the lipid in the cells will be released in the vascular walls (Portik-Dobos, Anstadt, Hutchinson, Bannan, & Ergul, 2002b). Factors like CRP, IL, serum factors etc. increases the breaking down of plaque which induces platelets. Thrombosis is formed and initiates many cerebrovascular complications Progressive diabetes can bring about micro and macro-vascular complications (Soejima et al., 2013). Diabetes brings about macro or micro vascular complications. Macro vascular complication includes atherosclerosis in cerebral artery, thrombotic obstructions and peripheral artery diseases (Barrett et al., 2017). Neuropathy is observed in micro vascular complications. Researchers have reported new information from post mortem reports on diabetic patients prone to cerebral small artery disease, lacunar infarction and ischemic stroke (Iso et al., 2004). Diabetic complications can be avoided with proper diet, physical exercises, nurturing mental health and controlling blood glucose level at all cost.

2. Hyperglycemia Induced Biochemical Mechanisms Responsible for Vascular Damage

The mechanisms underlying hyperglycemia-induced diabetic vascular damage focuses on five major mechanisms: increased flux of glucose and other sugars through the polyol pathway, increased intracellular formation of advanced glycation end-products (AGEs), increased expression of the receptor for advanced glycation end products and its activating ligands, activation of protein kinase C (PKC) isoforms, and over-activity of the hexosamine pathway (Brownlee, 2005), (Filla, Laura A.Edwards, 2016), (Wu, Yiang, Lai, & Li, 2018). It is necessary to ensure that more than one of these pathways is blocked.

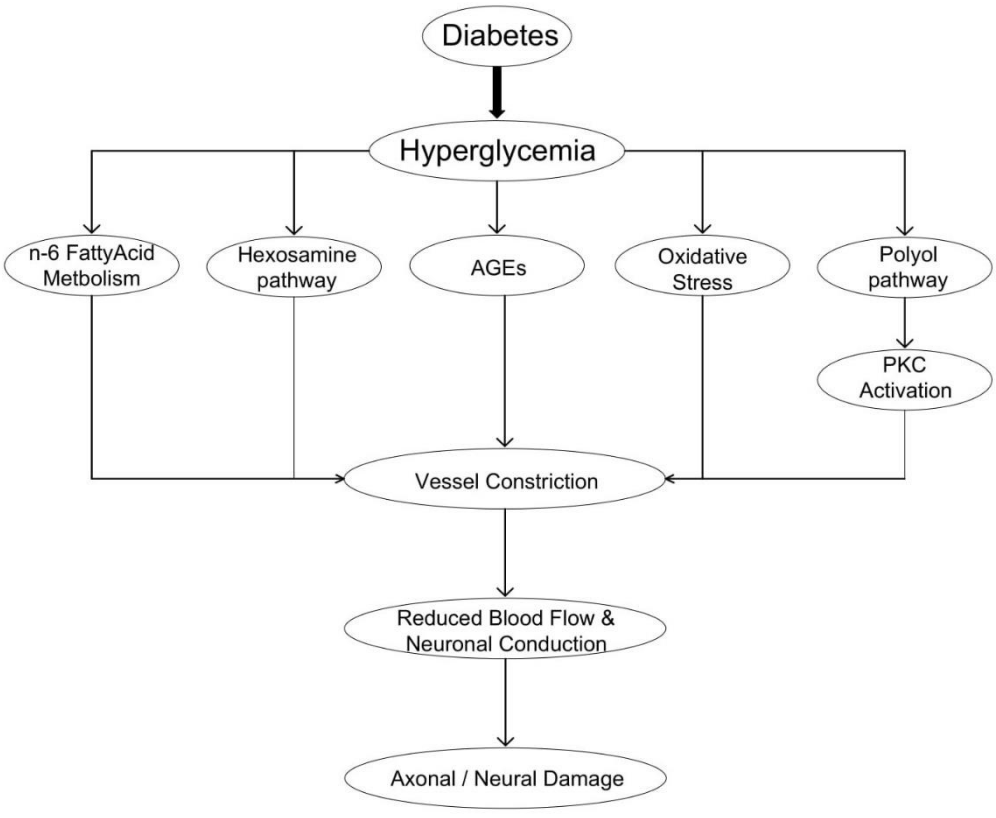

Figure 2: Progression of diabetic neuropathy

(Cobos-Palacios, Sampalo, & Carmona, 2020)

The above figure depicts the pathogenesis of diabetic neuropathy. Hyperglycemia triggers various mechanisms like polyol pathway, activates PKC, oxidative stress and the impaired n-6 fatty acid metabolism, generation of AGEs and auto oxidation of glucose. These results into reduced neurotrophic factors playing prominent role in neuro-restoring and neuro-protection, suppressing oxidation induced stress. By any means, reduction or removal of neurotrophic factors proportionately increases ROS and ultimately causes cell death through apoptosis. Neurotrophic factors decreases intracellular Ca^{2+} generated due to oxidative stress by increasing the expression of calcium-binding proteins or antioxidant enzymes. Vascular constriction, reduced blood flow, hypoxia, slow nerve conduction velocity etc. are the harmful events due to the above pathways which are co related to each other (Altschuler et al., 2013) , (Cobos-Palacios et al., 2020).

2.1 Polyol Pathway Flux

In the polyol pathway, glucose is converted into sorbitol in the presence of the enzyme, aldose reductase, which is then oxidized by the enzyme, sorbitol dehydrogenase (SDH), into fructose with the cofactor, NAD+. In hyperglycemic condition, the accumulation of sorbitol directly increases oxidative stress and indirectly due to NADPH increase, a cofactor regenerating reduced glutathione (GSH). As a result of polyol pathway, (Na+/K+) ATPase activity decreases which activates PKC pathway and glycative stress. (Sandireddy, Yerra, Areti, Komirishetty, & Kumar, 2014a).

2.2 Protein Kinase C Activation

When PKC is activated, it promotes the activity of cytosolic phospholipase A2. This later produces arachidonate and prostaglandin E2 (PGE2) which inhibits cellular (Na+/K+). Tissue is greatly injured through diabetes induced ROS when excessive PKC isoforms is formed. PKC

isoforms are also responsible for causing inflammation as it induces the mitogen activated protein kinases (MAPK) and nuclear factor kappa light chain enhancer of B cells (NF-κB) (Andjelkovic et al., 2020). Usually, PKC activation results into formation of DAG from glucose via triose phosphate while excessive rise of concentration of triose phosphate may rapidly form methyl glyoxal which is and diacylglycerol (DAG), which are a precursor of AGEs and an activator of PKC respectively (Vincent, Russell, Low, & Feldman, 2004). Thereafter, various complications such as, decreased nitric oxide (NO) production in smooth muscle cells and increased expression of fibrinolytic factor, plasminogen activator inhibitor (PAI-1), tumor growth factor-β (TGF-β), and NF-κB activation in cultured endothelial cells and in case of vascular smooth muscle cells are observed in excessive PKC activation (Rovira-Llopis et al., 2018).

2.3 Advanced Glycation End (AGE) Products

AGEs are responsible for damaging nerve fiber by AGE receptor ligation which can activate transcription of pleiotropic mediators NF-κB, later increases the yield of pro-inflammatory mediators (Ighodaro, Osasenaga, 2018). In hyperglycemic condition, AGE pathway is activated generating many AGE products specific to receptor for advanced glycation end products (RAGE) found in monocytes and endothelium cells (Tobon-Velasco, Cuevas, & Torres-Ramos, 2014). As a result, production of cytokines and adhesion molecules are observed with abnormal protein alteration and function. Circulatory AGEs and ROS/RNS increases in great extent.

2.4 Hexosamine Pathway Flux

In hexosamine pathway, glutamine fructose 6-phosphate amidotransferase (GFAT) converts fructose-6-phosphate to glucosamine-6-phosphate. In presence of specific O-GlcNAc

transferases glucosamine-6-phosphate is then converted into UDP-N acetyl glucosamine. Inhibiting GFAT blocks hyperglycemia-induced transcription of both TGF-α and TGF-β1. It has been observed in studies that hyperglycemia induces O-GlcN acylation of the transcription factor specificity protein 1 (Sp1) four times, which mediates hyperglycemia-induced activation of the plasminogen activator inhibitor-1 (PAI-1) promoter in vascular smooth muscle cells and of TGF-β1 and PAI-1 in arterial endothelial cells. PAI-1, TGF-α, and TGF-β1 activation leads to deposition of extracellular matrix which proceeds to neuroinflammation associated with diabetic neuropathy (Ighodaro, Osasenaga, 2018),(Sandireddy, Yerra, Areti, Komirishetty, & Kumar, 2014b).

3. Association between Diabetes and Cerebrovascular Dysfunction:

The progression of cerebrovascular diseases due to diabetes is still a controversy among the researchers and a great deal of attention has been paid in this field. Type-1 and Type-2 diabetes cause irregular insulin secretion and a hyperglycemic condition (McCrimmon, Ryan, & Frier, 2012). The Diabetes Control and Complications Trial (DCCT) in T1DM and the United Kingdom Prospective Diabetes Study (UKPDS) in T2DM showed the late onset and slow progression of diabetic micro vascular complications when the blood glucose is under control ("Implications of the Diabetes Control and Complications Trial," 2003) . Diabetes is a chronic disease where due to pancreas impairment insulin secretion is decreased or insulin resistance is established. Diabetes patients either suffering from macro or micro vascular diseases have cerebrovascular complications such as, ischemic stroke and hemorrhagic stroke (Portik-Dobos et al., 2002b). Hyperglycemic patients with type 2 diabetes have a greater risk for blood vessel damage by various pro-inflammatory mediators IL-6, TNF-α, soluble ICAM-1, and C-reactive protein (CRP). Treatment of cerebrovascular diseases becomes more complicated when patients have diabetes (Zhou et al., 2014). A study showed that women suffering from both type 1 and type 2 diabetes falls under 'very risky' category for ischemic stroke. The risk of stroke proportionately increases with time span of type 2 diabetes. Hemorrhagic stroke considered to be dreadful consequence of type 1 diabetes (Janghorbani et al., 2007).

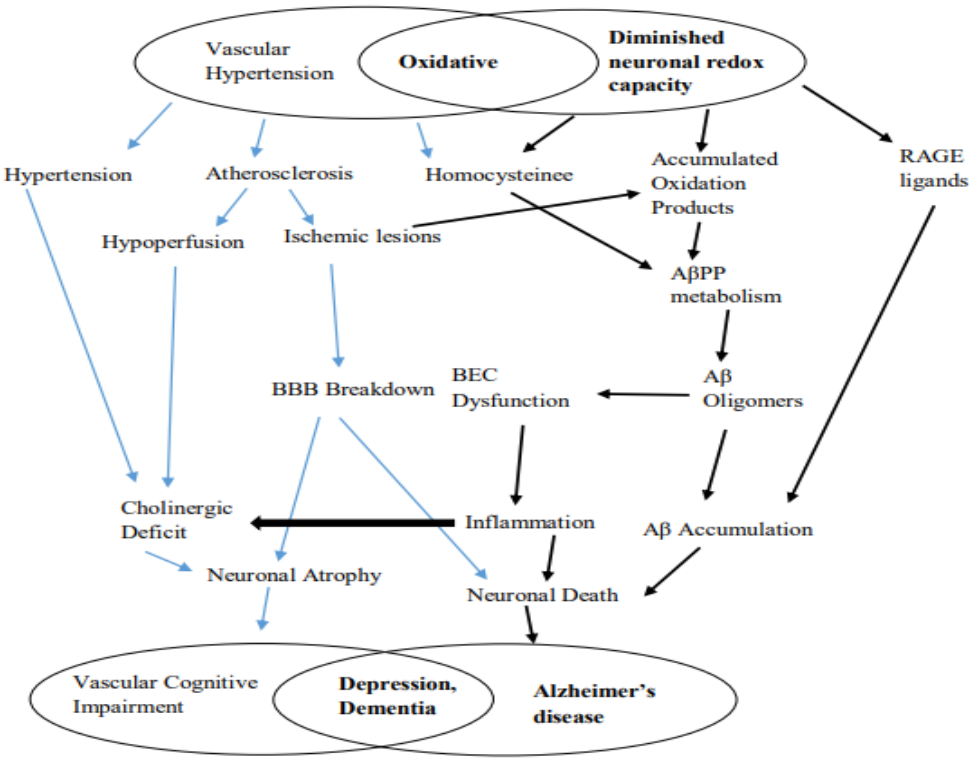

Figure 3: Oxidative stress inducing BBB hyperpermeabilty causing neuro-vascular impairment and neurological diseases like Alzheimer and dementia.

(Marlatt, Michael W., Lucassen, Paul J., Perry, George, Smith, Mark A., Zhu, 2008)

In the Figure 3, a clear depiction of the involvement of oxidative stress inducing the hyper-permeability of BBB has been shown. Vascular hypertension proportionately increases with oxidative stress which causes atherosclerosis, neuronal atrophy, and ischemic lesions primarily responsible for BBB breakdown, brain endothelium cells dysfunction, neuro-inflammation and neuronal death. Alzheimer's disease, depression, dementia are the ultimate results of hyper permeability of BBB.

Table 2: Reasons of Oxidative Stress in the Brain.

(Cobley et al., 2018):

Name	**Mechanistic Understanding**	**Disruptive Condition**	**Reference**
Redox-Signaling	NADPH oxidase2 (NOX2) derives O2- and H2O2. By P13K/Akt signaling NOX2 regulates the adult hippocampal progenitor cell growth	Inhibition or any abnormalities in NOX2 derived O_2^- and H2O2 can hinder neural progenitor and retinal cellular outgrowth	(Cobley et al., 2018), (Gauron et al., 2016)
Calcium Signaling	Regulates the neurotransmitters, neuro-synaptic plasticity	Excessive overload of Ca^{2+} can form $CO_3^{\cdot -}$ and $NO_2^{\cdot -}$, those are responsible for amyotrophic lateral sclerosis	(Franco et al., 2013), (Cobley et al., 2018)
Glutamate	Synthesize GABA neurotransmitter	Excessive glutamate causes excitotoxicity and by apoptotic signaling it causes neural cell death	(Raju et al., 2015), (Cobley et al., 2018)
Glucose	Glycolysis, energy generation	Methylglyoxal, highly reactive dicarbonyl compound is by product of glycolysis which produces AGEs and oxidative stress. Boosts AD and ischemia	(Allaman, Bélanger, & Magistretti, 2015)

4. Neuroinflammation

Studies suggest the concentration of peroxidizable polyunsaturated fatty acids and transition metals increase and antioxidant defense mechanism decreases when the brain suffers from oxidative stress (M., Maes, I., Mihaylova, M.,, Kubera, J.-C., Leunis, M., 2011). Chronic stress alters the normal homeostasis mechanism and poses threat to the neuronal cells. The investigation of post mortem reports revealed parallel contribution of oxidative stress and neuroinflammation in oxidative stress neurovascular dysfunction with blood-brain barrier hyper permeability (Burrage, Emily, Marshall, KentL, Santanam, Nalini, Chantler, 2018). Due to psychological stress antioxidants decrease and lipid peroxidation end products increase. Comparative studies between patients with unipolar depressive disorder and healthy subjects provided evidence of a rise in concentration of malondialdehyde and decreased nitrite, ascorbic acid and superoxide dismutase in the serum of patients diagnosed with unipolar disorder (Ng, Felicity, Berk, Michael, Dean, Olivia, Bush, 2008). Notable changes in peripheral markers of oxidation can be observed in depressed subjects. The activity of enzymes like glutathione peroxidase, catalase, and superoxide dismutase pro-oxidant enzyme (xanthine oxide) increases with inducible nitric oxide synthase (iNOS) and superoxide formation (M., Maes, I., Mihaylova, M.,, Kubera, J.-C., Leunis, M., 2011).

In many animal studies, pro-inflammatory mediators like Interleukin 6 (IL-6), Tissue Necrosis Factor- α (TNF- α), C - reactive protein (CRP) and Intercellular Adhesive Molecule -1 (ICAM-1) are observed to increase due to psychologically stressful events (Bernberg, Evelina, Ulleryd, Marcus A., Johansson, Maria E., Bergström, 2012). This is further validated by the role of pro-inflammatory cytokines in stress-induced vascular damage from its actions on the peripheral vasculature. As the pro- inflammatory cytokines increase, microglia and T-helper 1 cells are stimulated, altogether reducing concentration anti-inflammatory cytokines (Grippo, Angela J., Francis, Joseph, Beltz, Terry G., Felder, Robert B., Johnson, 2005). Oxidative stress sustain

due to the activation of microglia and acceleration of pro-inflammatory reactions by NF κB pathway. Vascular function is greatly affected due to reduction of NO signaling/ bioavailability, because a stressed brain with increased oxidative stress contributes to loss of cerebral micro vessel density (Yamamoto & Ando, 2011). Usually, NO synthase is exhibited in endothelial cells and astrocytes as eNOS and as nNOS in neurons. In normal conditions endothelial NOS (eNOS) and neuronal NOS (nNOS) nNOS are essential to regulate vascular smooth muscle tone and control release of neurotransmitter (Benoit, H., Jordan, M., Wagner, H., Wagner, 1999). But under stressful conditions with increased oxidative stress, the NO production is disrupted and its functionality is also obstructed since the beneficial endothelial NO synthase (eNOS) generation of NO is shifted to harmful superoxide generation from NO (ONOO-). This endothelial NO synthase (eNOS) generation of NO is essential to increase cellular cyclic guanosine monophosphate levels to increase cerebral blood flow through endothelial-dependent dilation (Lee et al., 2015). Besides, iNOS usually gets triggered under inflammatory environment. Now associating with super oxides, generation of iNOS and nNOS can invade the BBB by disrupting the vascular endothelial function (Song et al., 2020). However, ROS can inhibit NOS mRNA expression and eNOS activity by activating the PI3K/ras/Akt/MAPK pathway leading to redox gene expression (Lu, Yana, Li, Yihang, Li, Guang, Lu, 2020).

Furthermore, pro-inflammatory cytokines can reduce eNOS activity, expression and protein content thus affecting the endothelial functions. Apart from affecting the endothelium functions, they can also change calcium channel expression and up regulation of Rho- kinase expression and function (Patki, Solanki, Atrooz, Allam, & Salim, 2013). Reduction of antioxidant enzymes and calcium/calmodulin-dependent protein kinase type (CAMK) IV and an increase of extracellular signal-regulated kinase (ERK)-1/2 were observed in the hg hippocampus of the rats (Patki et al., 2013). Calcium (Ca^{2+}) is a second messenger which

maintains various important cellular processes and also link signaling between CaMKII and CaMKIV. The signaling mechanism plays an essential role in regulating contractile state and cellular growth to Ca^{2+} homeostasis and cellular permeability. Vascular tone increment is observed in oxidative stressed condition as ERK1/2 regulates the vascular smooth muscle constriction (Bhattacharya, Indranil, Damjanović, Marlen, Perez Dominguez, Ana, Haas, 2011). The study overall presents that stress alters normal functioning of the brain. Oxidative stress is responsible for microvascular rarefaction in the brain (Burrage et al., 2018).

4.1 Neuroinflammation and Role in Peripheral Nerve Damage

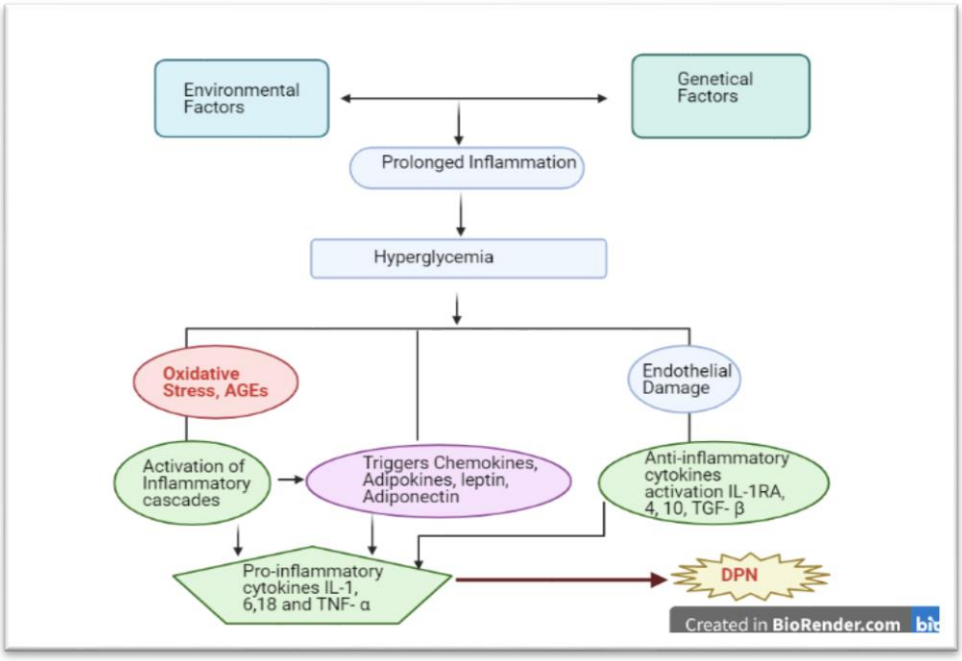

Figure 4: Association of chronic low grade inflammation in diabetic peripheral neuropathy (DPN) pathogenesis obtained from many experimental and clinical studies has been illustrated in the figure. Inflammatory markers and pro-inflammatory cytokines (IL--6, IL-1, tumor necrosis factor (TNF) -α and transforming growth factor-β) rises in DPN patients with pain. Besides, various pro-inflammatory cytokines, adipokines, chemokines and adhesion molecules performs significant role in signaling pathways. Henceforth, these inflammatory molecules are potential biomarkers of DPN.

(Kitada, Zhang, Mima, & King, 2010)

Long term hyperglycemic condition are considered to be the reason for neuroinflammation and nerve damage. Diabetic peripheral neuropathy is common in such condition causing sensory

loss and extreme neuropathic pain. The classical pathways such as; polyol pathway, PKC pathway, MAPK pathway, and increased production of AGEs could directly or indirectly trigger and progress the production of inflammatory mediators (Ighodaro, Osasenaga, 2018). AGEs are responsible for inducing the production of cytokines like IL-1, IL-6, IL-17, TNF-α, chemo attractant protein-1, C-reactive protein and chemokines like CCL-2, CXC, and so forth (Tobon-Velasco et al., 2014). AGEs acts on receptors present in microglia and macrophages. Inflammatory cascade is induced by the activation of RAGE due to NF-κB pathway induction. Furthermore, the up regulation of proinflammatory gene expression which initiates neuronal apoptosis is controlled by the transcription factor, NF-κB. NF-κB is also responsible for quenching the expression of antioxidant genes by down regulating Nrf-2 pathway and weakening the innate antioxidant defense (Tobon-Velasco et al., 2014). The structure of neuron is affected by inflammation due to hyperglycemia. The glycosylation of myelin protein changes its antigenicity causing infiltration of monocytes, macrophages, neutrophils from the blood circulation, and activation of glial cells of the nervous system (Sandireddy et al., 2014b). In response to such condition, inflammatory cytokines are secreted by these immune cells which causes damage to myelin sheath and increases the nerve excitability. The final consequence is edema and neuroinflammation. The peripheral receptors are sensitive by cytokines like IL-1, IL-6, and IL-17 which also causes nerve pain. Therefore, induction of monocytes and immune cells have a vicious positive feedback loop for increasing the production of inflammatory mediators thus potentiating nerve catastrophe (Vibha Shukla, Shakya, Perez-Pinzon, & Dave, 2017). Moreover, MAPK signaling pathway also potentiates nerve damage due to apoptosis. Besides, TNF-α reduces blood perfusion rate and therefore, decreases the neutrophic support by initiating the expression of cell adhesion molecules. Nerve cells have chemokine receptors which seen to be activated due to the release of chemokines and causes hyperalgesia (Barrett et al., 2017). Neuroinflammation is also accelerated by induction of inducible nitric oxide

synthase (iNOS) releasing NO, and increasing hypoxia and ischemia in diabetes. In all, inflammatory cascade initiation , proinflammatory cytokine up regulation, and neuroimmune communication pathways are primarily responsible in structural and functional damage of the peripheral nerves leading to the diabetic peripheral neuropathy (Sandireddy et al., 2014a).

Patients with depression are at a higher risk for development of DM following multiple pathways. ANS and HPA are activated in response to different stress stimuli causing change in immune system. People tend to lead a very unhealthy lifestyle, have poor quality food, exercise little or not at all and suffer from insomnia when they are stressed. Unhealthy lifestyle is a major cause of diabetes (Bonnet et al., 2005; Rod et al., 2009).

Additionally, smoking increases the risk of vascular endothelium dysfunction. Cigarette contains more than 4000 components among which ROS, nicotine and related pro-inflammatory activity are risk factors for stroke and cerebral infarction. Cigarette smoke extract (CSE) triggers a strong endothelial inflammatory response when the Blood Brain Barrier (BBB) is exposed. CSE also affects the functionality and coordinating ability of BBB followed by ischemic injury (Kaisar, Mohammad Abul, Prasad, Shikha, Cucullo, 2015). BBB gets hyper permeable due to neurovascular endothelial dysfunction (Burrage et al., 2018). Long term exposure to stress develops abdominal obesity since HPA and ANS functions actively, thus increasing the chances of diabetes (Björntorp, 2001; Vogelzangs et al., 2008).

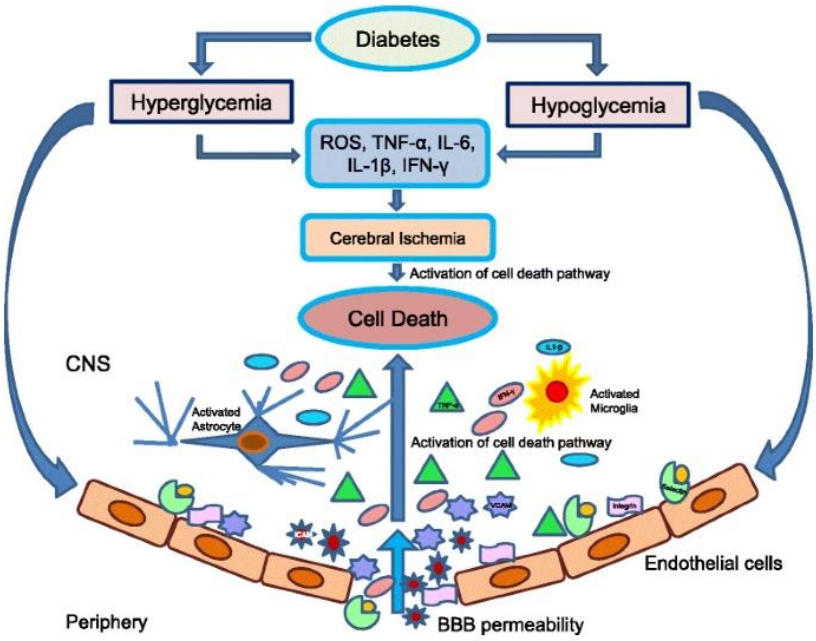

Figure 5: Schematic representation of neuroinflammation mechanisms involved in aggravating brain damage followed by cerebral ischemia under hyper and hypoglycemia

(Vibha Shukla et al., 2017)

There are distinct evidences of neuroinflammation and changes of immune system due to chronic stress. Several studies have reported increase in pro-inflammatory cytokines (IL-6, IL-8, IL-2, and CRP) under psychologically stressed or depressed conditions. The concentration of cortisol increases with activation of HPA, acting as a negative feedback mechanism to cope with stress. Pro-inflammatory cytokines and cortisol are responsible for changes of mood and behavior (Leonard and Myint, 2009). This activated immune system can trigger the neurotransmitter and neuroendocrine secretion by stress mediators (Berge & Riise, 2015). According to Pickup (2004), hypercytokinemia and triggered innate immunity are responsible for sleep disturbance and depression. He also claimed the association of cytokine-induced acute-phase response and pathogenesis of type 2 diabetes (Bădescu et al., 2016), (Pouwer, Kupper, & Adriaanse, 2010). In the Figure 5, diabetic patients under stressful environment undergoes similar condition and usually cerebral infarction and atherosclerosis are observed in these patients.

5. Participation of Various Signaling Pathways in CVD Progression:

In diabetes and pre diabetes, brain is the target end organ. Several co-morbidities like hypertension, obesity, cardiovascular diseases exist simultaneously. Cerebrovascular disease is a major co-morbidity. A study showed the association of diabetes with increased risk of stroke was 1.5-2.0 fold. With a stroke the relative-risk increased by1.15 (95% CI 1.08–1.23) for every 1% rise in HbA1c (McCrimmon et al., 2012). Prognosis of type-2 diabetes can be due to genetic or life style changes which ultimately causes oxidative stress.

Chronic oxidative stress in diabetes can alter the mitochondrial genetic material and nuclear DNA leading to mitochondrial dysfunction that accelerates huge production of ROS (Sifuentes-Franco, Pacheco-Moisés, Rodríguez-Carrizalez, & Miranda-Díaz, 2017). Production of ROS and activation of NF-kB pathway unchains an increase of pro-inflammatory cytokines AGE receptors are activated is activated and produced ROS which triggers NF-KB pathway during hyperglycemia. The consequence is BBB impairment and neurological damage (Pooja Naik, 2014).

Consequently, NF-KB is activated and attracts the pro-inflammatory cytokines and macrophages to adhere in the vessels initiating plaque formation, later atherosclerosis (Marchio et al., 2019). Oxidative stress and inflammation together causes endothelium disruption and ROS generation (Marchio et al., 2019). A very recent review stated that Wnt/c-Jun N-terminal kinase signaling is responsible in endothelial dysfunction, triggering the inflammatory cytokines and insulin resistance (Chen et al., 2021).

MAPK/ERK mediated activity is observed during insulin resistant condition thereby the amount of pro-inflammatory markers (PAI-1, ICAM-1, VCAM-1, and E-selectin) increases and causing endothelium dysfunction (Janus, Szahidewicz-Krupska, Mazur, & Doroszko, 2016).

Table 3: List of Transcription Factors and Proteins causing Atherosclerosis and Cerebrovascular Dysfunction.

Transcription factor	Description	Impaired Condition	Reference
TCF7L2	Transcription factor 7-like 2, also known as TCF7L2 or TCF4, is a protein acting as a transcription factor that, in humans, is encoded by the TCF7L2 gene.	Conditional deletion of Tcf7l2 in adipocytes leads to glucose intolerance and adipocyte hypertrophy.	(Geoghegan et al., 2019)
NF-kB	Nuclear factor	induction of pro-inflammatory cytokines, chemotactic factors and adhesion molecules, thereby promoting monocyte recruitment and atherosclerosis progression	(Liu, Ting, Zhang, Lingyun, Joo, Donghyun, Sun, 2017)

SREBP	Sterol regulatory element binding proteins	Lipogenesis, obesity and glucose resistance, cholesterol and cerebral impairment	(Leoni & Caccia, 2015)
(HIF)-1a	Hypoxia-inducible factor	High glucose-induced blood-brain barrier (BBB) permeability, hypoxic neurons, glucose intolerance	(Xiao, Gu, Wang, & Zhao, 2013)
GATA-4.	Transcription factor GATA-4 is a protein that in humans is encoded by the GATA4 gene	Vascular inflammation and atherosclerosis	
SGK1	Serum- and glucocorticoid-regulated kinase 1 (SGK1), a glucocorticoid receptor (GR) target gene.	Due to chronic stress, it affects hippocampal neurogenesis, damages oligodendrocytes.	(Anacker et al., 2013)

PPARG	PPARG (Peroxisome Proliferator Activated Receptor Gamma) is a protein Coding gene	Post Stroke neuronal death, oxidative stress inflammation, obesity	(Vemuganti, 2008)
STAT3	Signal transducer and activator of transcription 3 is a transcription factor which in humans is encoded by the STAT3 gene	Inflammation, oxidative stress, obesity	(Mohammad, H., Marchisella, F., Ortega-Martinez, S., Hollos, P., Eerola, K., Komulainen, E., Kulesskaya, N., Freemantle, E., Fagerholm, V., Savontous, E., Rauvala, H., Peterson, B. D., Van Praag, H., Coffey, 2018)
CXCR4	C-X-C chemokine receptor type 4 also known as fusin or CD184 is a protein	Increases macrophage accumulation,	(Vidaković et al., 2015)

	that in humans is encoded by the CXCR4 gene.	inflammatory cytokine production, insulin resistance	
ICAM-1	Intercellular adhesion molecule-1, a protein encoded by ICAM-1 gene	Endothelium dysfunction, oxidative stress	(Vibha Shukla et al., 2017)
VCAM-1	Vascular cell adhesion molecule-1 (VCAM-1), a protein encoded by VCAM gene	induce procoagulatory changes on and increase the adhesion of inflammatory cells to the endothelium cell surface, later leads to atherosclerosis	(Kaisar, Mohammad Abul, Prasad, Shikha, Cucullo, 2015), (Giacco & Brownlee, 2010)

Different studies on severely depressed patients and stressed induced rodent models showed the consistent rise of glucocorticoid hormones. This rise of glucocorticoid hormones can affect the hippocampal neurogenesis. Serum- and glucocorticoid-regulated kinase 1 (SGK1), a glucocorticoid receptor (GR) target gene is responsible responding to cellular stress and

neuronal functioning. During stress and subsequent rise of glucocorticoids, SGK1 expression increases in human neural stem cells and in rodent neurons. Acute stress increases excitability and working memory by activating SGK1. Up-regulation of SGK1 in murine corpus callosum causes damage in the morphology of oligodendrocytes due to chronic stress. SGK1 can be targeted to develop antidepressants (Anacker et al., 2013).

The review also investigated the genetic abnormalities both inherited and occurred due to the exposure of other complications. In diabetic mice, HDAC3 activity and expression in the hippocampus and cortex were increased. HDAC3 inhibition can prevent diabetes induced hyper-permeability of BBB. Any disruption in Nfr2 regulation may mediate oxidative/inflammatory stress-induced neurovascular dysfunction and BBB dysfunction. In cultured human brain microvascular endothelial cells, it showed that HDAC3 inhibition repressed Keap1 through miR-200a upregulation, thereby reducing Keap1-Nrf2 interaction and promoting Nrf2 activation. HDAC3 inhibition helps blood glucose control and pancreatic β-cell function as well (Zhao et al., 2019). It can thus be said that HDAC3 may possibly be a new therapeutic target to protect BBB during diabetes.

Mutations in NOTCH 3 genes in arteriole smooth muscle cells and mutations in HTRA1 are the reasons of cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (Zhao et al., 2019. Recurrent stroke and permanent impairment are a significant result caused due to this inherited mutation. Diabetes worsen these cerebral small vessel disease conditions by disrupting the blood supply, BBB damage and lacunar infarctions (Awad & Polster, 2019).

6. KEGG Pathway Analysis:

Whenever we try to find the crosstalk among various diseases, pathway analysis is mandatory since it investigate the relationship among them. Now a days, scientist are more inclined towards bioinformatics, a collection of biological, chemical and genomic information. In this review we have selected Kyoto Encyclopedia of Genes and Genomes (KEGG) as it provides information of protein and gene participating in the pathways, phosphorylation/ activation/ inhibition among nodes, cross-link between diseases (Kanehisa et al., 2008). The use of KEGG pathway analysis is preferable as we can obtain the network of cellular functions and regulations involving interconnected pathways, represent it graphical and also aim at precise target of the pathways (Keshava Prasad, T. S., Goel, Renu, Kandasamy et al., 2009).

6.1 ROS-Activated MAPK signaling pathway

The reactive oxygen species during cellular oxidative stress is prominently responsible for inciting ERKs, JNKs, or p38 MAPKs (Son et al., 2011). In a recent KEGG analysis study it was found that MAPK and Ras1 signaling pathway were both associated with diabetes (Feng et al., 2019). MAPK pathway consisting of almost 257 genes, in oxidative stressed condition gets triggered and thus an inflammatory environment is created (Feng et al., 2019)

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The p38 mitogen-activated protein kinase (MAPK) is considered to be involved in development of atherosclerosis and aortic valve sclerotic lesions as in different cell type it can incite inflammation triggered by chemokine and oxidative stress (Reustle & Torzewski, 2018).

The mitogen-activated protein kinase (MAPK) cascade is a highly conserved module that is involved in various cellular functions, including cell proliferation, differentiation and migration. Mammals express at least four distinctly regulated groups of MAPKs, extracellular signal-related kinases (ERK)-1/2, Jun amino-terminal kinases (JNK1/2/3), p38 proteins (p38alpha/beta/gamma/delta) and ERK5 that are activated by specific MAPKKs: MEK1/2 for ERK1/2, MKK3/6 for the p38, MKK4/7 (JNKK1/2) for the JNKs, and MEK5 for ERK5. Each MAPKK, however, can be activated by more than one MAPKKK, increasing the complexity and diversity of MAPK signalling. Presumably each MAPKKK confers responsiveness to distinct stimuli. For example, activation of ERK1/2 by growth factors depends on the MAPKKK c-Raf, but other MAPKKKs may activate ERK1/2 in response to pro-inflammatory stimuli (KEGG PATHWAY: map04010, 2020).

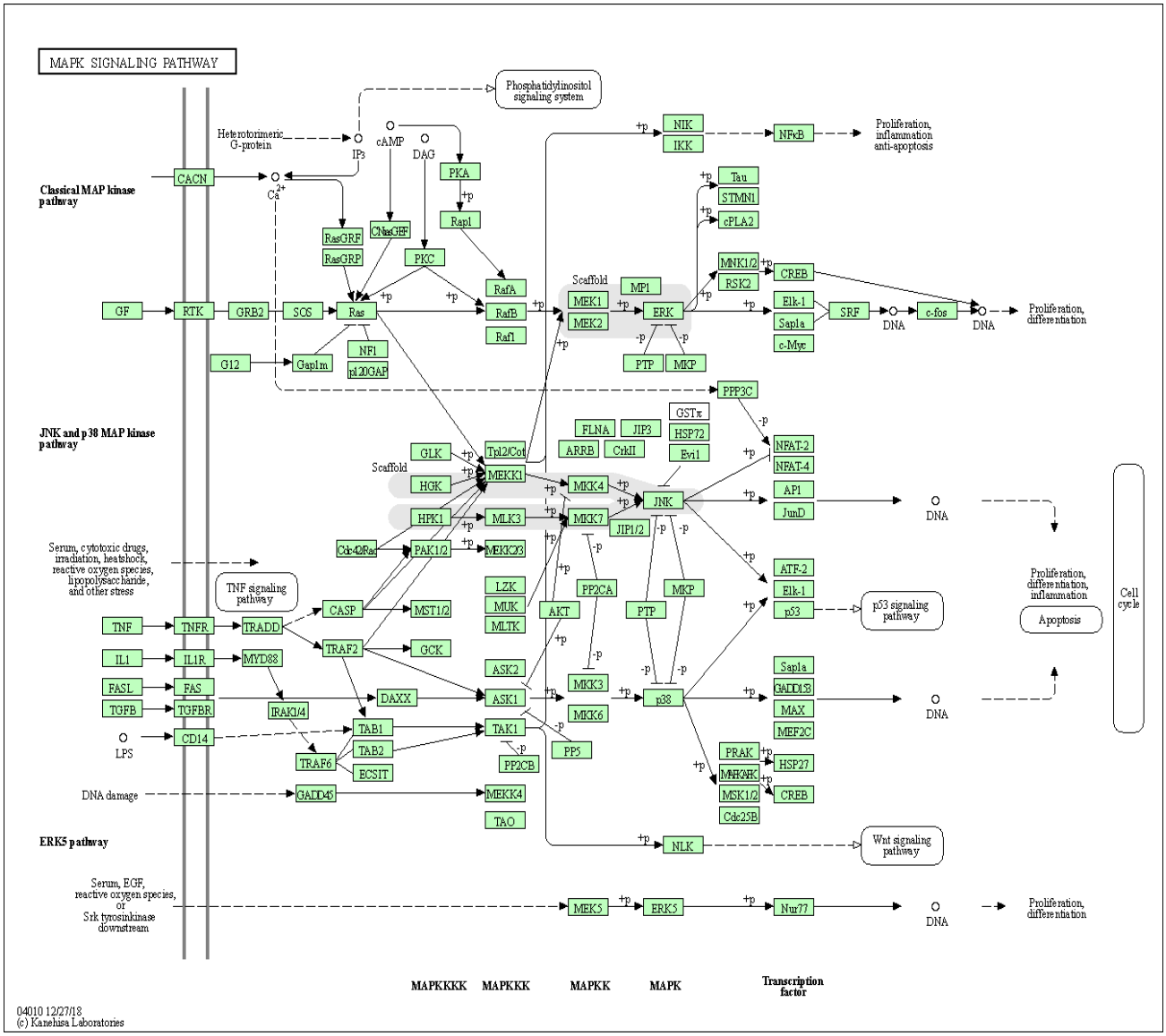

Figure 6: KEGG pathway analysis (KEGG PATHWAY: map040s10, 2020).

7. Conclusion

Diabetes is a common and chronic metabolic disease hampering the quality of life. Persistent hyperglycemia causes damage to the whole body including tissues, organs and even nervous system. During the past several decades, major neurological disorders such as ischemic stroke, cognitive dysfunction, intracerebral hemorrhage etc. are observed in diabetic condition coupled with chronic depression and stress (Sandireddy et al., 2014a), (Ross, 1999). Various pathways are implicated in progression of oxidative stress which creates an imbalance in pro-oxidant/antioxidant homeostasis that leads to the generation of toxic ROS. ROS can inhibit NOS mRNA expression and eNOS activity by activating the PI3K/ras/Akt/MAPK pathway leading to redox gene expression (Lu, Yana, Li, Yihang, Li, Guang, Lu, 2020). The crosstalk between diabetes induced oxidative stress and cerebrovascular dysfunction. MAPK, chemokine, adipocytokine, calcium, JakSTAT, PI3K etc. signaling pathways are commonly implicated for neuronal death and atherosclerosis (Janus et al., 2016). Gene regulatory network is an integrated network model system which dissects diseases at genetic levels, also establishes the appropriate connections among various genes and therefore, provides the linkages of different diseases causing cerebral dysfunction with hyperglycemia and stress. Impairment due to various transcription factors such as; TCF7L2, NF-kB, SREBP, (HIF)-1a, GATA-4, SGK1, PPARG, STAT3, STAT3, ICAM-1, VCAM-1 were observed due to hyperglycemia induced oxidative stress causing atherosclerosis which is prominently responsible for cerebral dysfunction and ischemic stroke (Jesmin, Rashid, Jamil, Hontecillas, & Bassaganya-Riera, 2010), (Grant, 2019), (Xiao et al., 2013), (Newsholme, Cruzat, Keane, Carlessi, & De Bittencourt, 2016). The role of pro-inflammatory cytokines (IL-6, IL-8, IL-2, and CRP) are potential biomarkers of oxidative stress which causes neuroinflammation (Zhou et al., 2014). Oxidative stress, triggered in the early phase of ischemic brain injury, plays an important role in pathogenesis and evolution of the vascular lesions. By and large, the detailed study of

inflammatory and pro-inflammatory mediators, various pathways of diabetes prognosis and an integrated gene regulatory network analysis can precisely detect the cause/mechanism behind the cerebrovascular dysfunction in hyperglycemia.

There are lack of experiments and research on hyperglycemia induced cerebrovascular dysfunction. The biomarkers of oxidative stress could be helpful (Barnham, Masters, & Bush, 2004) and preventive interventions is essential. The use of bioinformatics has opened doors to study in detail, thus the neuroprotective molecules and genetics have received attention for designing precise medication (Barnham et al., 2004).

The molecular markers could be measured in biological samples in the clinical laboratory, alongside the genetic study can more precisely provide a feasible therapy which can target certain pathway and thus acting as a pleiotropic drug (Mendes Arent, André, Souza,, Luiz Felipe De, Walz, Roger, Dafre, 2014). Future study could also be directed to find the mechanism of early protection BBB of a disease (Song et al., 2020).

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